Supplementary appendix

This supplement contains the following items:

1. Search Strategy
2. Summary of included trials
3. Supplementary Figures

Search Strategy

Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 8 of 12, 2012) in The Cochrane Library (705 hits in CENTRAL)

#1 MeSH descriptor Hetastarch explode all trees

#2 ((hydroxyet*yl and starch) or (HES and "130") or tetrastarch or hetastarch or Voluven or Volulyte or Tetraspan or Venofundin or Equihes or ISOHES or Restorvol or Venohes or Amidolite or Hesra)

#3 (#1 OR #2)

MEDLINE (Ovid SP)(1946 to September 2012)(2151 hits)

1. ((hydroxyet*yl and starch) or (HES and 130) or tetrastarch or hetastarch or Voluven or Volulyte or Tetraspan or Venofundin or Equihes or ISOHES or Restorvol or Venohes or Amidolite or Hesra).mp. [mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

2. exp Hetastarch/

3. 1 or 2

EMBASE (Ovid SP)(1974 to September 2012)(3758 hits)

1. exp HETASTARCH/

2. ((hydroxyet*yl and starch) or (HES and 130) or tetrastarch or hetastarch or Voluven or Volulyte or Tetraspan or Venofundin or Equihes or ISOHES or Restorvol or Venohes or Amidolite or Hesra).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer]

3. 1 or 2

4. limit 3 to human

Science Citation Index Expanded (http://apps.webofknowledge.com)(1900 to September 2012)(3259 hits)

1 3,259 TS=((hydroxyet*yl and starch) or (HES and "130") or tetrastarch or hetastarch or Voluven or Volulyte or Tetraspan or Venofundin or Equihes or ISOHES or Restorvol or Venohes or Amidolite or Hesra)

BIOSIS Previews (http://apps.webofknowledge.com)(1969 to September 2012)(1395 hits)

3 1,395 #2 OR #1

2 598 TI=((hydroxyet*yl and starch) or (HES and "130") or tetrastarch or hetastarch or Voluven or Volulyte or Tetraspan or Venofundin or Equihes or ISOHES or Restorvol or Venohes or Amidolite or Hesra) AND Taxa Notes=(Humans)

1 1,395 TS=((hydroxyet*yl and starch) or (HES and "130") or tetrastarch or hetastarch or Voluven or Volulyte or Tetraspan or Venofundin or Equihes or ISOHES or Restorvol or Venohes or Amidolite or Hesra) AND Taxa Notes=(Humans)

CINAHL (EBSCO host)(1981 to November 2011)(279 hits)

S3 S1 or S2

S2 TX ((hydroxyet*yl and starch) or (HES and 130) or tetrastarch or hetastarch or Voluven or Volulyte or Tetraspan or Venofundin or Equihes or ISOHES or Restorvol or Venohes or Amidolite or Hesra)

S1 MM hydroxyethyl starch

6S-trial

Methods	• **Design:** RCT • **Setting:** Multicenter • **Blinding:** Yes

Participants	• **Country:** Denmark, Norway, Finland, Iceland
	• **Inclusion criteria:** Adults, severe sepsis and need of fluid resuscitation
	• **Surgical / medical:** 29% surgical, 71% medical
	• **Number of patients:**
	  ○ Group 1: 398
	  ○ Group 2: 400
	• **Age (median, IQR):**
	  • Group 1 : 66 (56-75)
	  • Group 2: 67 (56-76)
	• **SAPS II-score (median, IQR):**
	  • Group 1 : 50 (40-60)
	  • Group 2: 51 (39-62)
	Exclusion criteria: <18 y of age, RRT, kidney or liver transplantation, burn injury >10% of body surface, intracranial bleeding, serum potassium >6 mmol per liter within 6 hr before screening, included in another ICU trial, withdrawal from active therapy, received >1000 ml of synthetic colloid,

Interventions	• **Indication:** Fluid resuscitation, judged by the clinican, no predefined targets • **Dosing:** Max. 33 ml/kg/day. • **Intervention period:** ICU-stay, max. 90 day **Group 1:** • 6% HES 130/0.4 in Ringer's Acetate (Tetraspan®) • Total volume: 3000 (IQR: 1507-5100) **Group 2:** • Ringer's Acetate • Total volume 3000 (IQR: 2000-5750)
Outcomes	1.1 Overall mortality 1.2 RRT at end of follow-up 2.1 RRT 2.2 Creatinine x 2 2.3 RBC transfusion 2.4 Volume of transfused RBC 2.5 Bleeding episodes 2.6 Blood loss 2.7 Severe Adverse Reactions

	Time frame: 90 days for mortality and RRT. ICU-stay for other outcomes.	
Notes		
Risk of bias		
Bias	**Authors judgement**	**Support for judgement**
Random Sequence Generation	Low	Computer-generated
Allocation Concealment	Low	Phone/web-based randomisation
Blinding	Low	Blinded
Incomplete Outcome Data - mortality	Low	No missingness
Incomplete Outcome Data – other outcomes	Low	Missingness adequately described
Selective Outcome reporting	Low	
Baseline Imbalance	Low	No imbalance
Bias due to vested financial interests	Low	Funded by the Danish Research Councils. B Braun Medical delivered trial fluids to the trial sites free of charge. The contract between B Braun Medical AG and the sponsor ensures publication of the trial results independently of B Braun Medical AG.
Academic bias	Low	No previous trials on HES

BaSES (unpublished)

Reference: http://clinicaltrials.gov/ct2/show/NCT00273728

Methods	• **Design:** RCT • **Setting:** 2 ICUs in one hospital • **Blinding:** Yes

Participants	• **Country:** Switzerland
	• **Inclusion criteria:** Adults, with sepsis. Hypotension, oliguria or altered mental state could replace SIRS-criteria
	• **Number of patients:**
	  ○ Group 1: 117
	  ○ Group 2: 124
	• **Age (median, IQR):**
	  • Group 1 : 67 (50-75)
	  • Group 2: 68 (60-75)
	• **SOFA-score (median, IQR):**
	  • Group 1 : 3 (1-6)
	  • Group 2: 3 (1-6)
	• **APACHE II-score (median, IQR):**
	  • Group 1 : 21 (14-27)
	  • Group 2: 22 (13-28)
	Exclusion criteria: Pregnancy, age > 18y, allergy against HES products, chronic or acute kidney injury with Crea > 350 µmol/l

Interventions	• **Indication:** Fluid resuscitation. • **Dosing:** Every litre of study fluid was followed by one litre of Ringer's lactate. • **Intervention period:** 5 days **Group 1:** • HES 130/0.4 in Saline (Voluven®) • Total volume (median, IQR): 3775ml (2018-6347) • Additional Ringer's lactate (median, IQR): 5354ml (3015-8933) **Group 2:** • Isotonic Saline • Total volume (median, IQR): 4125ml (2500-6730) • Additional Ringer's lactate (median, IQR): 5770ml (3244-9930)
Outcomes	1.1 Overall mortality 1.2 RRT at end of follow-up 2.1 RRT **Time frame:** 1 year

Notes		
Risk of bias		
Bias	**Authors judgement**	**Support for judgement**
Random Sequence Generation	Low	Computer-generated
Allocation Concealment	Low	
Blinding	Low	Blinded
Incomplete Outcome Data - mortality	Low	No missingness
Incomplete Outcome Data – other outcomes	-	No data on other outcomes
Selective Outcome reporting	Low	Renal data has been registered and awaits publication.
Baseline Imbalance	Low	
Bias due to vested financial interests	Low	Fresenius Kabi delivered study fluids for free and paid for the packaging and blinding process. A signed contract between Fresenius and sponsor states that sponsor is free to publish all data without influence from Fresenius.
Academic Bias	Low	No previous studies on HES 130/0.4.

CHEST

Methods	• **Design:** RCT • **Setting:** Multicenter • **Blinding:** Yes	

Participants	• **Country:** Australia, New Zealand
	• **Inclusion criteria:** Adults patients in the ICU, need of fluid resuscitation. Predefined subgroup of patients with sepsis (n=1937)
	• **Number of patients:**
	  ○ Group 1: 979 (total: 3500)
	  ○ Group 2: 958 (total: 3500)
	• **Age, all patients (mean ± SD):**
	  • Group 1: 63 ± 17
	  • Group 2: 63 ± 17
	• **APACHE II-score, all patients (median, IQR):**
	  • Group 1 : 17 (12-22)
	  • Group 2: 17 (12-23)
	Exclusion criteria: <18 y of age, known allergy to starch, intracranial hemorrhage, RRT ongoing or imminent, creatinine > 350µmol/l, women aged 18-49 y unless negative pregnancy test, received >1000 ml starch already, cardiac surgical patients, burns, liver transplantation, imminent or inevitable death, underlying disease with a life expectancy of < 90 d, already received resuscitation fluid in the ICU, therapy limitations.	

Interventions	• **Indication:** Fluid resuscitation. • **Dosing:** 50 ml/kg/day • **Intervention period:** ICU-stay, max. 90 days **Group 1:** • HES 130/0.4 in Saline (Voluven®) • Daily volume in the first 4 days, all patients (mean ± SD): 526 ± 425 **Group 2:** • Isotonic Saline • Daily volume in the first 4 days, all patients (mean ± SD): 616 ± 488	
Outcomes	1.1 Overall mortality **Time frame:** 90 days	
Notes	Renal data of the sepsis subgroup are still unpublished.	
Risk of bias		
Bias	**Authors judgement**	**Support for judgement**
Random Sequence Generation	Low	Computer-generated

Allocation Concealment	Low	
Blinding	Low	Blinded
Incomplete Outcome Data - mortality	Low	Missingness < 1%
Incomplete Outcome Data – other outcomes	-	No data on other outcomes
Selective Outcome reporting	Low	Renal data has been registered and awaits publication.
Baseline Imbalance	Low	
Bias due to vested financial interests	Low	Fresenius Kabi supplied the study fluids and distributed them to participating sites. The trial was partly financed by an unrestricted grant from Fresenius Kabi. However, Fresenius Kabi had no input into the design, conduct, data collection, statistical analysis or writing of the manuscript.
Academic Bias	Low	No previous studies on HES 130/0.4.

CRYSTMAS

Other references:

Data published on clinicaltrials.gov

http://clinicaltrials.gov/ct2/show/NCT00464204

FDA Package insert (May 2, 2012)
http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/NewDrugApplicationsNDAs/ucm082785.htm

Methods	• **Design:** RCT • **Setting:** Multicenter • **Blinding:** Yes

Participants	• **Country:** France, Germany
	• **Inclusion criteria:** Adults, severe sepsis and need of fluid resuscitation
	• **Number of patients:**
	  ○ Group 1: 100
	  ○ Group 2: 96
	• **Age (mean ± SD):**
	  • Group 1 : 65.8 ± 15.4
	  • Group 2: 65.9 ± 14.7
	Exclusion criteria: creatinine > 300 µM, chronic renal failure, anuria > 4 hours, RRT

Interventions	• **Indication:** Fluid resuscitation • **Dosing:** Max. 50 ml/kg on day 1. Max. 25 ml/kg days 2 to 4. • **Intervention period:** 4 days **Group 1:** • HES 130/0.4 in saline (Voluven®) • Total volume (mean ± SD): 2615 ± 1499 **Group 2:** • Isotonic Saline • Total volume (mean ± SD): 2788 ± 1799
Outcomes	1.1 Overall mortality 2.1 RRT 2.2 Creatinine x 2 2.3 RBC transfusion 2.4 Volume of transfused RBC 2.6 Blood loss 2.7 Severe Adverse Events **Time frame:** Mortality, RRT and Severe Adverse Events: 90 days. Other endpoints: ICU-stay

Notes	Data on dialysis were not reported in the publication, but were retrieved from the FDA package insert for Voluven. Data on blood loss and haemorrhage were delivered by Fresenius Kabi: **Haemorrhage** Voluven: 9 of 100 Saline: 10 of 96 Observation period: 8 days **Blood loss** Voluven: 468 ± 1454 in 100 patients Saline: 456 ± 1398 in 96 patients Observation period: 4 days	
Risk of bias		
Bias	**Authors judgement**	**Support for judgement**
Random Sequence Generation	Low	Reply from author
Allocation Concealment	Low	Reply from author
Blinding	Low	Reply from author
Incomplete Outcome Data – mortality	Low	All patients were analysed
Incomplete Outcome Data – other outcomes	Low	All patients were analysed
Selective Outcome reporting	Low	All outcomes of relevance to this review are reported in either the paper or in the FDA package insert or retrieved from the authors. However, one nutrition outcome was changed from primary to secondary on clinicaltrials.gov after end of trial.
Baseline Imbalance	Low	
Bias due to vested financial interests	High	Conducted by the manufacturer of Voluven®, Fresenius Kabi AG
Academic Bias	High	Primary investigator has previously made smaller studies of HES and published reviews of HES focusing on effectiveness of HES 130/0.4 and the few

		adverse effects compared with other starches.

Dolecek 2009

Methods	• **Design:** RCT • **Setting:** Single center • **Blinding:** No

Participants	• **Country:** Czech Republic
	• **Inclusion criteria:** Adults with severe sepsis on the ventilator. Extra vascular lung water index > 7 ml/kg as measured by PiCCO.
	• **Surgical / medical:** both
	• **Number of patients:**
	  ○ Group 1: 26
	  ○ Group 2: 30
	• **Age (mean, range):**
	  • Group 1 : 43 (23-67)
	  • Group 2: 47 (19-81)
	• **SOFA-score (mean ± SD):**
	  • Group 1 : 8.8 ± 3.0
	  • Group 2: 8.0 ± 2.0
	
	Exclusion criteria: severe coagulopathy, pregnancy, cardiac failure, AKF, limitations for PiCCO - aortic aneurism, severe aortal regurgitation, dysrythmia

Interventions	• **Indication:** Fixed dose • **Dosing:** see below. • **Intervention period:** 3 days **Group 1:** • HES 130/0.4 in saline (Voluven®). • Total volume: 4 x 250 ml per day in 3 days **Group 2:** • Albumin 20% • Total volume: 2 x 100 ml per day in 3 days
Outcomes	1.1 Overall mortality 1.2 RRT at end of follow-up 2.1 RRT 2.2 Creatinine x 2 2.7 Severe Adverse Reactions **Time frame:** mortality: 28 days; RRT, creatinine and serious adverse events: 3 days
Notes	The authors now work in another hospital and have no longer access to source data on renal replacement therapy, bleeding or blood transfusions.
Risk of bias	

Bias	Authors judgement	Support for judgement
Random Sequence Generation	Low	Computer generated, mail from author
Allocation Concealment	Low	Sealed envelopes
Blinding	Low for mortality and creatinine / high for RRT if we get these data	Unblinded treatment, but study fluid was given in fixed doses.
Incomplete Outcome Data - mortality	Low	CONSORT diagram in paper
Incomplete Outcome Data – other outcomes	Low	
Selective Outcome reporting	Low	
Baseline Imbalance	Low	No imbalance
Bias due to vested financial interests	Low	None declared
Academic Bias	Low	

Dubin 2010

Methods	• **Design:** RCT • **Setting:** 2 centers • **Blinding:** No

Participants	• **Country:** Argentina
	• **Inclusion criteria:** Adults, sepsis and tissue hypoperfusion
	• **Surgical / medical:** both
	• **Number of patients:**
	  ○ Group 1: 12
	  ○ Group 2: 13
	• **Age (mean ± SD):**
	  • Group 1 : 62 ± 21
	  • Group 2: 65 ± 12
	• **SOFA-score (mean ± SD):**
	  • Group 1 : 8.1 ± 2.5
	  • Group 2: 8.9 ± 3.6
	
	Exclusion criteria: Not possible to perform lingual videomicroscopy, < 18y, pregnancy, stroke, acute coronary syndrome, hydrostatic pulmonary edema, status astmaticus, cardiac arrhythmias, contraindication for central venous catheterization, active gastrointestinal haemorrhage, seizures, drug intoxication, burns, trauma, need of imidiate surgery, terminal cancer, immunosuppression, no resuscitation order, delayed admission til ITA (more than 4 hours), previous resuscitation with > 1500 ml fluid

Interventions	• **Indication:** Fluid resuscitation • **Dosing:** NS • **Intervention period:** 24 hours **Group 1:** • HES 130/0.4 in saline (Voluven®) • Total volume (mean ± SD): 2610 ± 885 **Group 2:** • Isotonic saline • Total volume (mean ± SD): 6254 ± 2603
Outcomes	1.1 Overall mortality 1.2 RRT at 90 days 2.1 RRT 2.2 Creatinine x 2 2.3 RBC transfusion 2.4 Volume of transfused RBC

	2.7 Severe Adverse Reactions **Time frame:** Mortality 28 days. Other outcomes: 24 hours.	
Notes		
Risk of bias		
Bias	**Authors judgement**	**Support for judgement**
Random Sequence Generation	Low	Computer-generated
Allocation Concealment	Low	Sealed envelopes
Blinding	High	No blinding
Incomplete Outcome Data - mortality	Low	Consort diagram in paper
Incomplete Outcome Data – other outcomes	Low	
Selective Outcome reporting	Low	
Baseline Imbalance	Low	No imbalance
Bias due to vested financial interests	Low	None declared
Academic Bias	Low	

Lv 2012

Methods	• **Design:** RCT • **Setting:** Single center • **Blinding:** Unclear	

Participants	• **Country:** China
	• **Inclusion criteria:** Septic shock, > 18 years old, > 30 ml/kg fluid received in 24 hours,
	• **Number of patients:**
	  ○ Group 1: 22
	  ○ Group 2: 20
	• **Age** (mean ± SD)**:**
	  • Group 1 : 66 ± 15
	  • Group 2: 65 ± 14
	Exclusion criteria: Blood products received in the last 24h, history of bleeding or coagulation disorder, receiving drug with potential impact on coagulation.	

Interventions	• **Indication:** Fluid resuscitation • **Dosing:** Max. dose not defined. • **Intervention period:** 24 hours **Group 1:** • 6% HES 130/0.4 (unknown carrier solution) • Total volume (mean ± SD): 2.8 ± 0.6 **Group 2:** • Ringer's lactate • Total volume (mean ± SD): 3.5 ± 0.7	
Outcomes	1.1 Overall mortality **Time frame:** Not specifically stated, but appears to be the entire ICU stay	
Notes		
Risk of bias		
Bias	**Authors judgement**	**Support for judgement**
Random Sequence Generation	Low	"Random table"
Allocation Concealment	High	Not described
Blinding (RRT, transfusion)	Unclear	Not mentioned
Incomplete Outcome Data - mortality	Unclear	Not stated that there were no dropouts
Incomplete Outcome Data – other outcomes	-	No data
Selective Outcome reporting	Low	Mortality and ICU length of stay are accounted for. No detailed information on kidney function.
Baseline Imbalance	Low	

Bias due to vested financial interests	Unclear	
Academic Bias	Unclear	

Palumbo 2006

Methods	• **Design:** RCT • **Setting:** Single center • **Blinding:** Unclear	

Participants	• **Country:** Italy
	• **Inclusion criteria:** Severe sepis
	• **Surgical / medical:** 7 medical, 13 surgical
	• **Number of patients:**
	  • Group 1: 10
	  • Group 2: 10
	• **Age (mean ± SD):**
	  • All patients: 59.6 ± 12.6
	• **APACHE (mean ± SD):**
	  • All patients: 19.0 ± 3.6
	
	Exclusion criteria: < 21 years, renal dysfunction (serum creatinin > 2.0 mg/dl, blood nitrogen > 150 mg/dl, urine output < 20 ml/h in spite of diuretic therapy with furosemide), severe liver failure, DIC syndrome, considered to be in terminal state	

Interventions	• **Indication:** To maintain capillary wedge pressure • Dosing: NS • **Intervention period:** NS, but probably 5 days **Group 1:** • HES 130/0.4 in saline (Voluven®) • Total volume: NS **Group 2:** • Albumin: 20% • Total volume: NS	
Outcomes	No data included in the review	
Notes		
Risk of bias		
Bias	**Authors judgement**	**Support for judgement**
Random Sequence Generation	Unclear	Not reported
Allocation Concealment	High	Not reported, “assigned in a randomized sequence”
Blinding	Unclear	Not stated
Incomplete Outcome Data - mortality	Low	All patients followed-up
Incomplete Outcome Data – other outcomes	-	No other outcomes reported.
Selective Outcome reporting	High	Mortality is reported for

		each single patient without group assignment. Kidney function not reported.
Baseline Imbalance	Low	“groups were homogeneous for age, sex and pathology”
Bias due to vested financial interests	Unclear	Not stated
Academic Bias	Low	

Zhu 2011

Methods	• **Design:** RCT • **Setting:** Single center • **Blinding:** No	

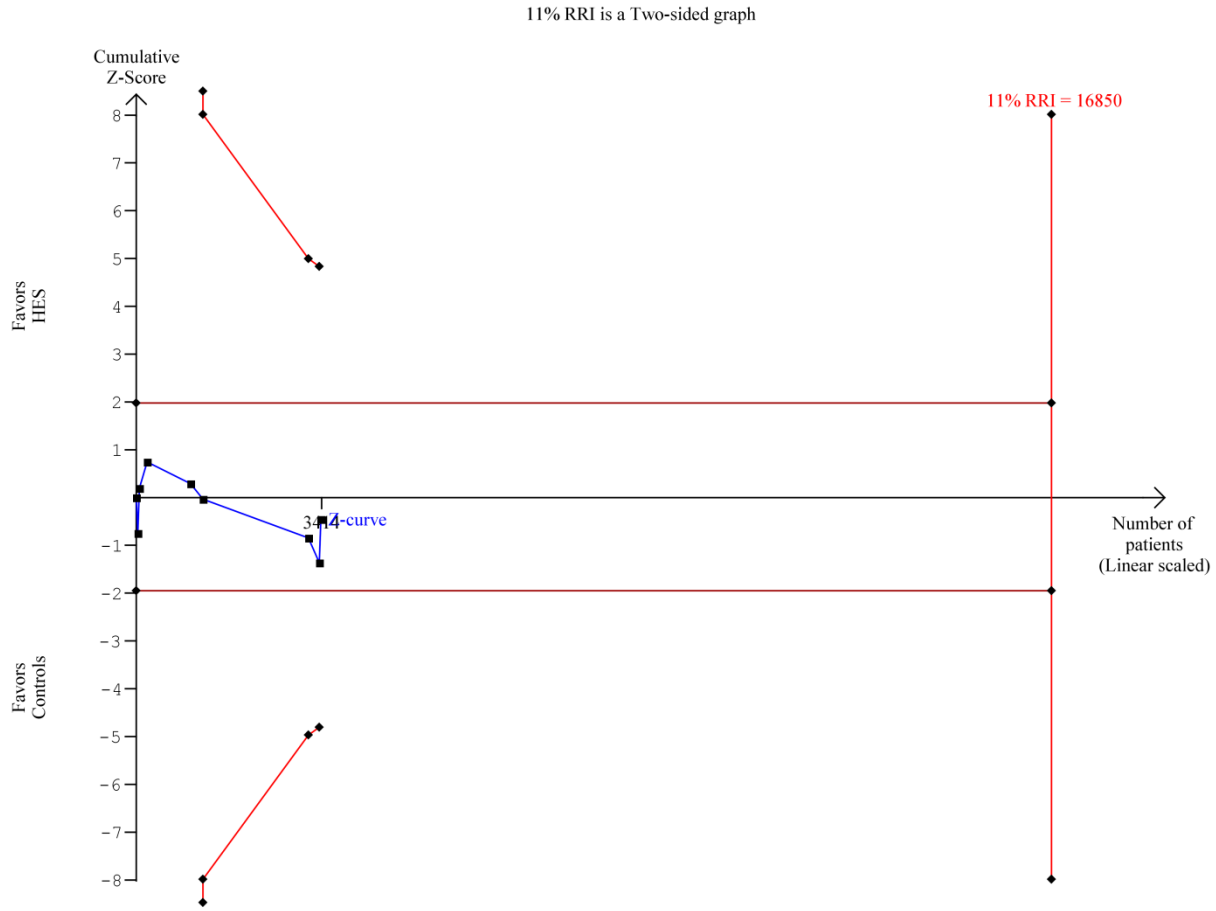
Participants	• **Country:** China
	• **Inclusion criteria:** Severe sepsis, adults
	• **Surgical / Medical:** all medical
	• **Number of patients:**
	  ○ Group 1: 45
	  ○ Group 2: 45
	  ○ Group 3: 45
	• **Age (mean ± SD):**
	  • Group 1 : 59.4 ± 8.8
	  • Group 2: 59.9 ± 9.4
	  • Group 3: 59.8 ± 9.3
	• **APACHE II-score (mean ± SD):**
	  • Group 1 : 17.3 ± 1.8
	  • Group 2: 17.0 ± 1.6
	  • Group 3: 17.2 ± 1.7
	Exclusion criteria: < 21 years, creatinine > 450 µmol/l, severe liver dysfunction, DIC or end-stage disease.	

Interventions	• **Indication:** Fluid resuscitation • **Dosing:** NS • **Intervention period:** Until urine output > 1 ml/kg for 1 hour OR 24 hours **Group 1:** • HES 130/0.4 in hypertonic saline • Total volume: 5476 ± 209 **Group 2:** • HES 130/0.4 in saline • Total volume: 6383 ± 287 **Group 3:** • Ringer's lactate • Total volume: 7439 ± 230	
Outcomes	1.1 Overall mortality **Time frame:** 24 hours.	
Notes		
Risk of bias		
Bias	**Authors judgement**	**Support for judgement**
Random Sequence Generation	Unclear	Not stated
Allocation Concealment	High	Not stated
Blinding	High	
Incomplete Outcome Data - mortality	Unclear	Not stated that there

		were no dropouts
Incomplete Outcome Data – other outcomes	-	No data
Selective Outcome reporting	Low	Mortality and organ failures are accounted for. No detailed information on kidney function.
Baseline Imbalance	Low	
Bias due to vested financial interests	Low	Financial support from Pharmaceutical Health Research Program of Hubei province
Academic Bias	Unclear	

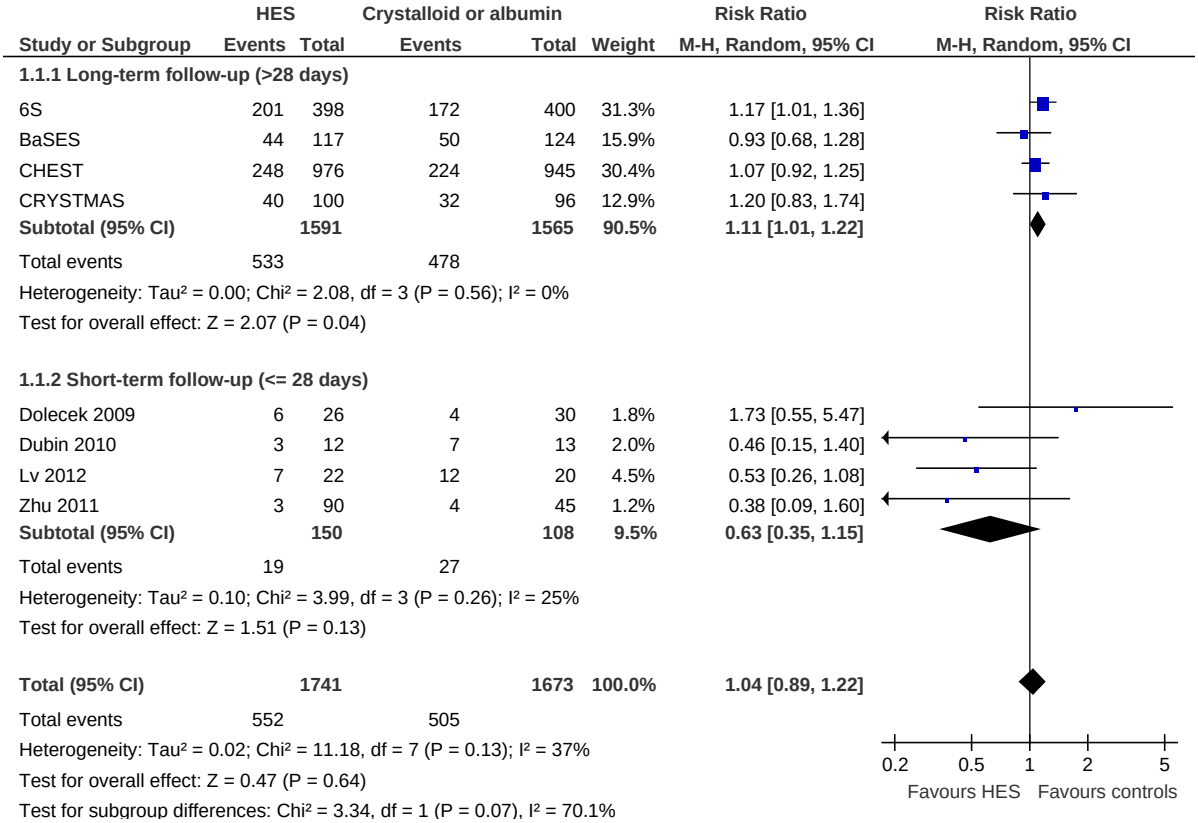
Supplementary figures

Trial Sequential Analysis of mortality in all trials

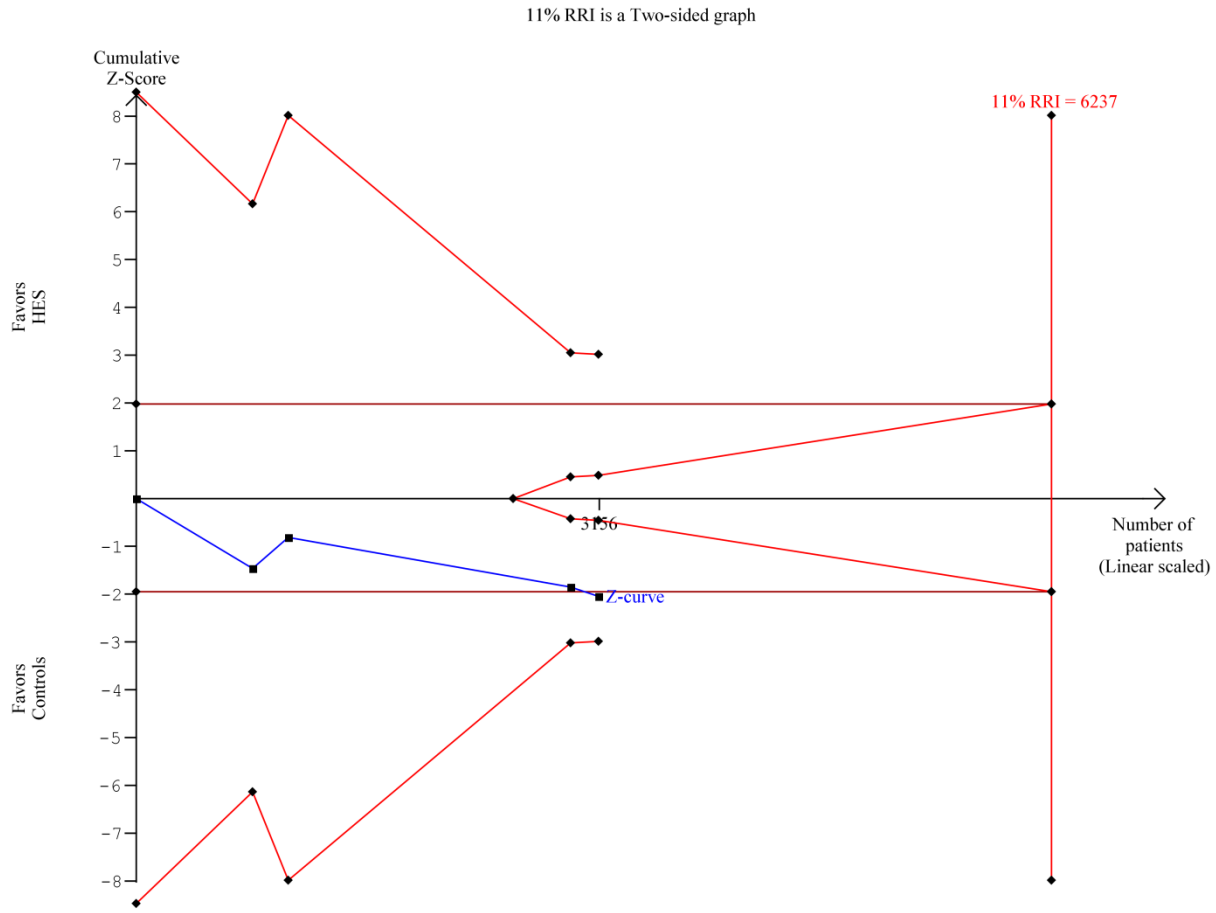


We calculated a diversity-adjusted information size of 16850 patients using α = 0.05 (two-sided), β = 0.20 (power = 80%), D^2= 63%, an anticipated relative risk increase of 11% and an event proportion of 30% in the control arm. The cumulative z-curve (blue) was constructed using a random-effects model. Only approximately 20% of the required information size was reached. The TSA adjusted confidence interval was 0.70 to 1.54.

Forest plot of trials with long-term (> 28 days) follow-up vs. trials with short-term follow-up (≤ 28 days)

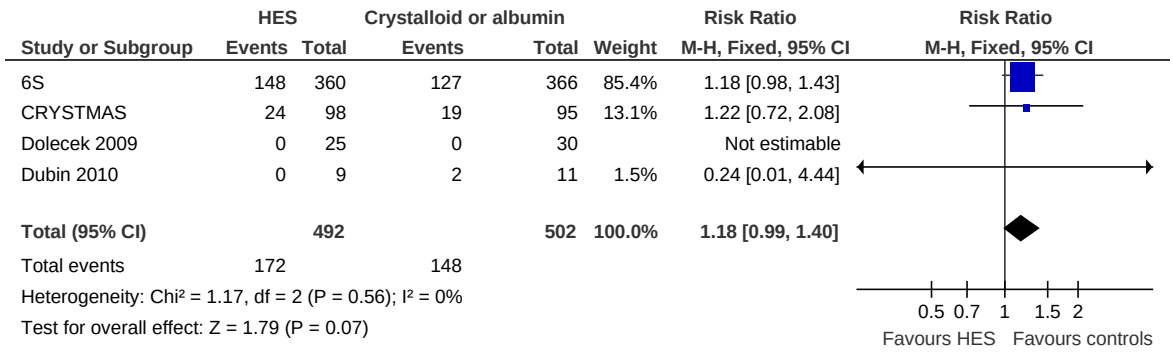


Trial Sequential Analysis of mortality in trials with follow-up for more than 28 days



We calculated a diversity-adjusted information size of 6237 patients using α = 0.05 (two-sided), β = 0.20 (power = 80%), D^2= 0%, an anticipated relative risk increase of 11% and an event proportion of 30% in the control arm. The cumulative z-curve (blue) was constructed using a random-effects model. The required information size was not reached and the z-curve crossed the conventional boundary, but not the trial sequential monitoring boundary for harm. The TSA adjusted confidence interval was 0.95 to 1.29. The z-curve needs to pass through the futility area to reach the area of benefit leaving little chance that HES will turn out to reduce the relative risk of death with 11% if further trials are conducted in patients with sepsis.

Forest plot of acute kidney injury (two-fold increase in creatinine)

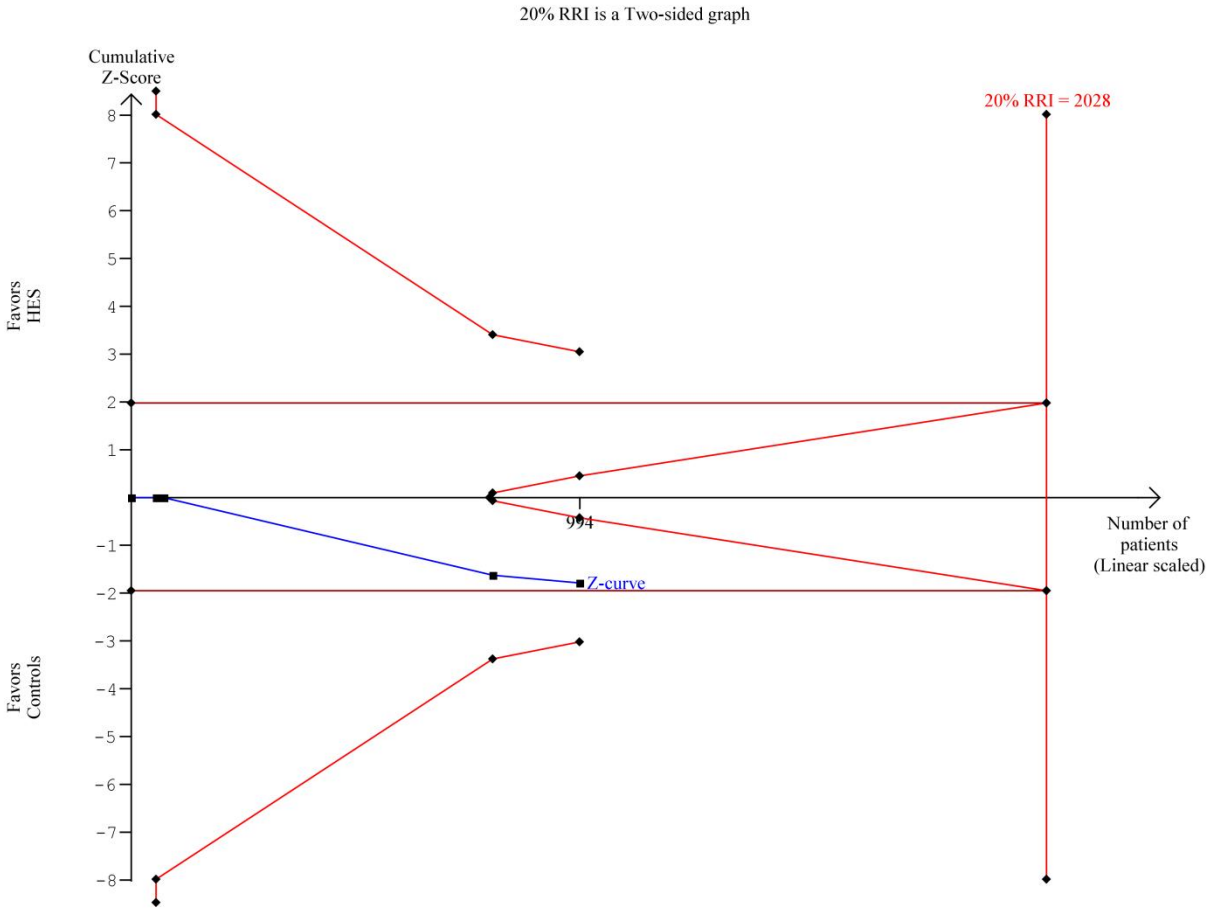


Study or Subgroup	HES Events	HES Total	Crystalloid or albumin Events	Crystalloid or albumin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6S	148	360	127	366	85.4%	1.18 [0.98, 1.43]
CRYSTMAS	24	98	19	95	13.1%	1.22 [0.72, 2.08]
Dolecek 2009	0	25	0	30		Not estimable
Dubin 2010	0	9	2	11	1.5%	0.24 [0.01, 4.44]
Total (95% CI)		**492**		**502**	**100.0%**	**1.18 [0.99, 1.40]**
Total events	172		148			

Heterogeneity: Chi² = 1.17, df = 2 (P = 0.56); I² = 0%

Test for overall effect: Z = 1.79 (P = 0.07)

Trial sequential analysis of acute kidney injury (two-fold increase in creatinine)



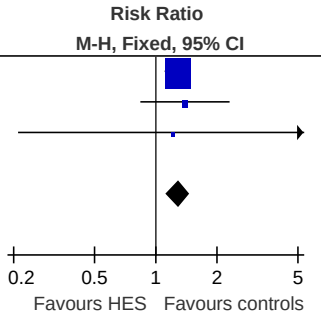
We calculated a diversity-adjusted information size of 2028 patients using α = 0.05 (two-sided), β = 0.20 (power = 80%), D^2= 0%, an anticipated relative risk increase of 20% and an proportion rate of 29% in the control arm. The cumulative z-curve (blue) was constructed using a fixed-effects model. Trials with no events were included in the analysis with an empirical continuity correction of 0.01. The required information size was not reached, and the z-curve did not cross the trial sequential monitoring boundary for harm. The TSA adjusted confidence interval was 0.90 to 1.54.

Forest plot of transfusion with red blood cells

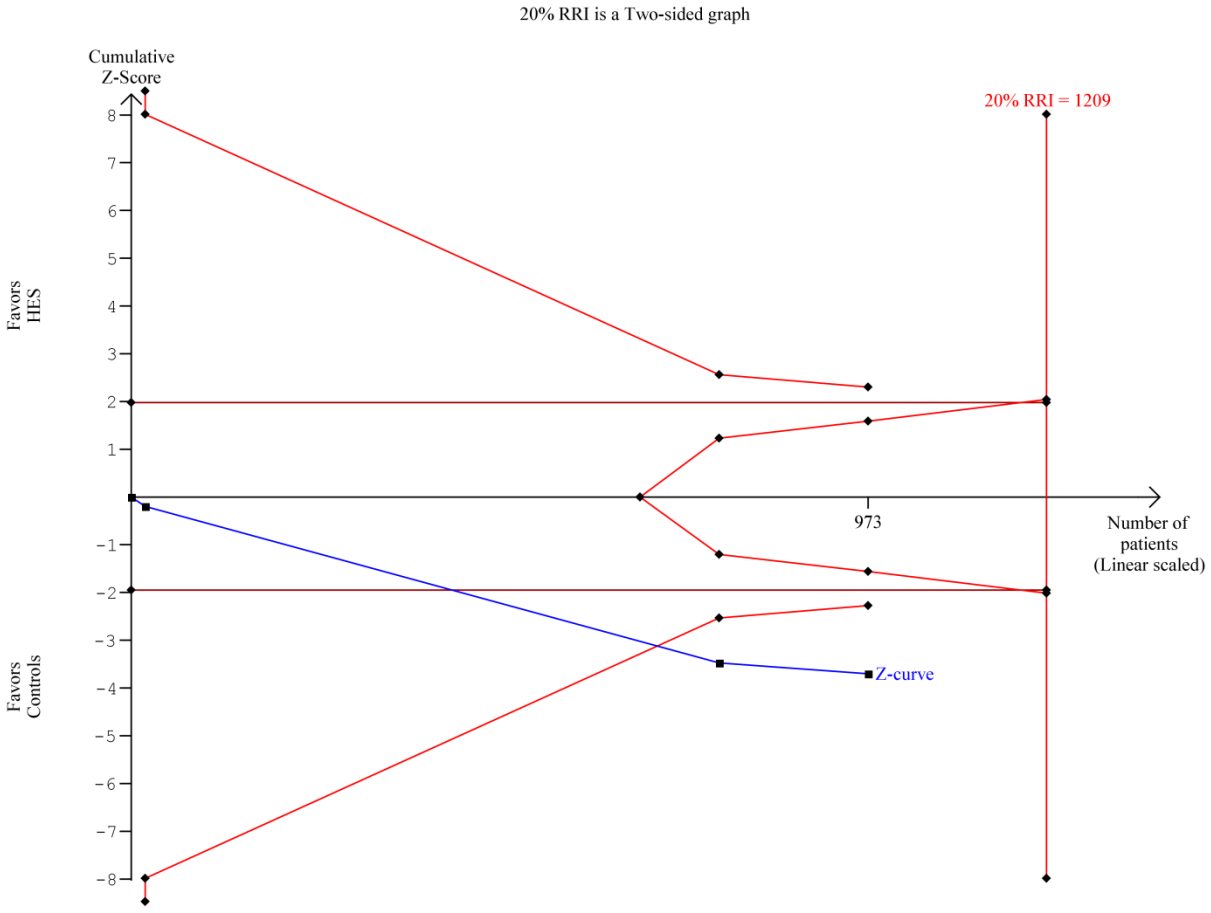
Study or Subgroup	HES Events	HES Total	Crystalloid or albumin Events	Crystalloid or albumin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6S	220	377	173	380	88.6%	1.28 [1.12, 1.47]
CRYSTMAS	29	100	20	96	10.5%	1.39 [0.85, 2.29]
Dubin 2010	2	9	2	11	0.9%	1.22 [0.21, 7.04]
Total (95% CI)		**486**		**487**	**100.0%**	**1.29 [1.13, 1.48]**
Total events	251		195			

Heterogeneity: Chi² = 0.10, df = 2 (P = 0.95); I² = 0%

Test for overall effect: Z = 3.73 (P = 0.0002)



Trial sequential analysis of transfusion with red blood cells



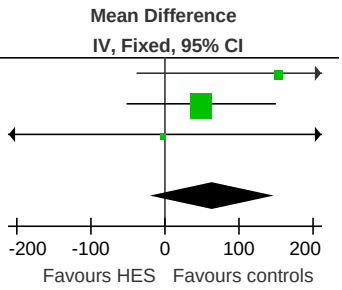
We calculated a diversity-adjusted information size of 1209 patients using α = 0.05 (two-sided), β = 0.20 (power = 80%), D^2= 0%, an anticipated relative risk increase of 20% and an event proportion of 40% in the control arm. The cumulative z-curve (blue) was constructed using a fixed-effects model. The required information size was not reached, but the z-curve crossed the trial sequential monitoring boundary for harm and the TSA adjusted confidence interval was 1.10 to 1.51 providing firm evidence of increased use of red blood cell transfusion in patients treated with HES vs. crystalloid or albumin.

Forest plot of volume of red blood cell transfusion

Study or Subgroup	HES Mean	HES SD	HES Total	Crystalloid or albumin Mean	Crystalloid or albumin SD	Crystalloid or albumin Total	Weight	Mean Difference IV, Fixed, 95% CI
6S	810	1,442	377	657	1,218	380	19.5%	153.00 [-37.22, 343.22]
CRYSTMAS	214	358	100	165	354	96	71.2%	49.00 [-50.69, 148.69]
Dubin 2010	133	265	9	136	364	11	9.3%	-3.00 [-279.12, 273.12]
Total (95% CI)			**486**			**487**	**100.0%**	**64.51 [-19.60, 148.61]**

Heterogeneity: Chi² = 1.15, df = 2 (P = 0.56); I² = 0%

Test for overall effect: Z = 1.50 (P = 0.13)

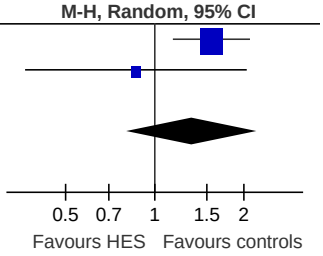


Forest plot of bleeding episodes

Study or Subgroup	HES Events	HES Total	Crystalloid or albumin Events	Crystalloid or albumin Total	Weight	Risk Ratio M-H, Random, 95% CI
6S	93	398	60	399	74.4%	1.55 [1.16, 2.08]
CRYSTMAS	9	100	10	96	25.6%	0.86 [0.37, 2.03]
Total (95% CI)		**498**		**495**	**100.0%**	**1.34 [0.81, 2.21]**
Total events	102		70			

Heterogeneity: Tau² = 0.07; Chi² = 1.62, df = 1 (P = 0.20); I² = 38%

Test for overall effect: Z = 1.13 (P = 0.26)

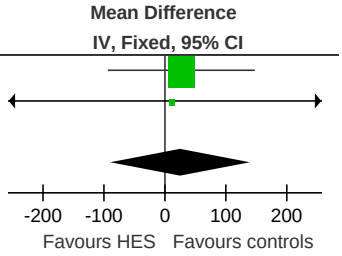


Forest plot of blood loss

Study or Subgroup	HES Mean	HES SD	HES Total	Crystalloid or albumin Mean	Crystalloid or albumin SD	Crystalloid or albumin Total	Weight	Mean Difference IV, Fixed, 95% CI
6S	192	799	398	165	915	399	91.8%	27.00 [-92.26, 146.26]
CRYSTMAS	468	1,454	100	456	1,398	96	8.2%	12.00 [-387.27, 411.27]
Total (95% CI)			**498**			**495**	**100.0%**	**25.77 [-88.50, 140.04]**

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.94); I² = 0%

Test for overall effect: Z = 0.44 (P = 0.66)

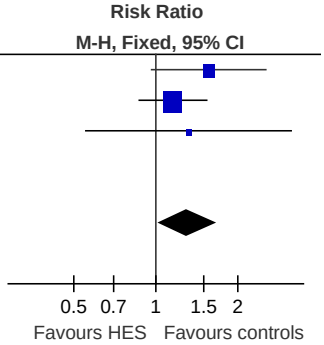


Forest plot of severe adverse events

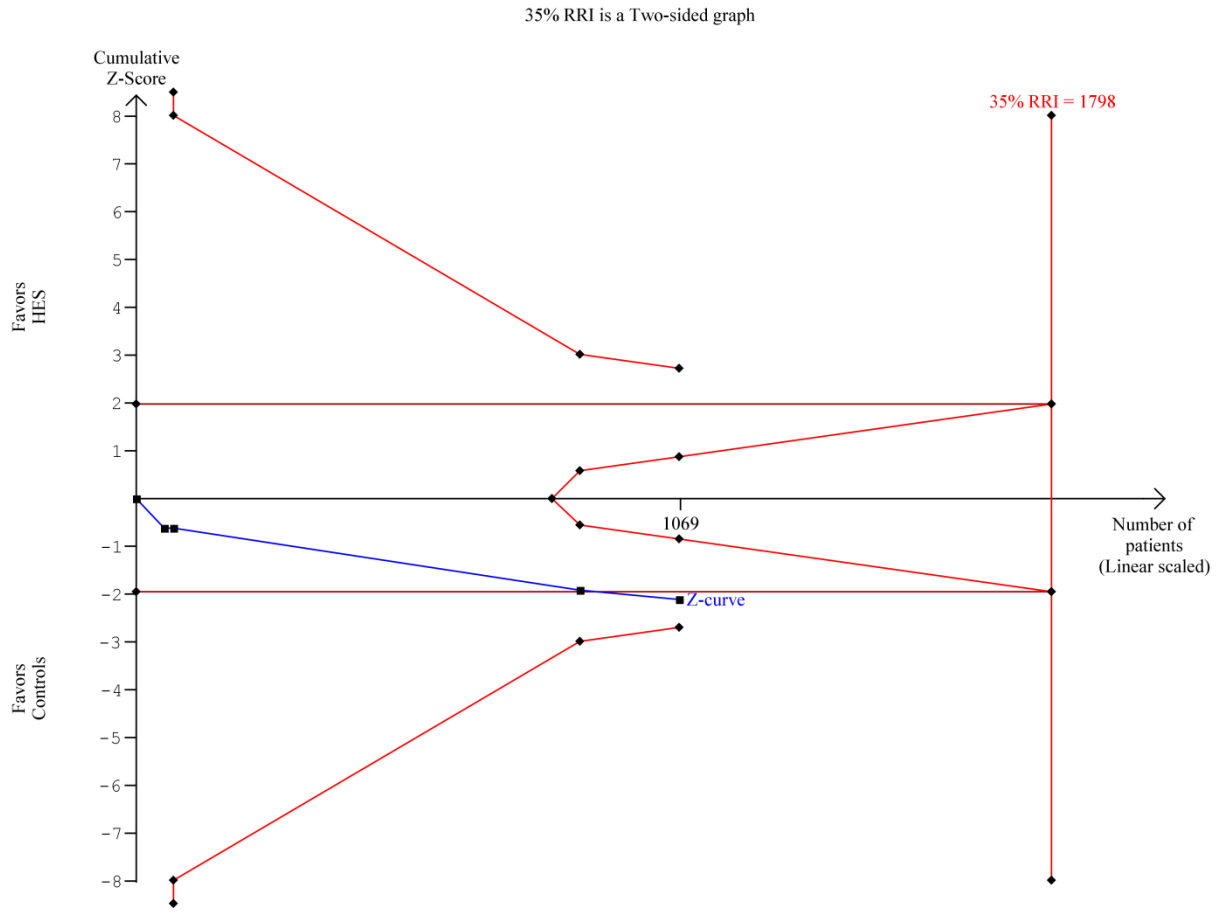
Study or Subgroup	HES Events	HES Total	Crystalloid or albumin Events	Crystalloid or albumin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6S	39	398	25	399	32.7%	1.56 [0.97, 2.53]
CRYSTMAS	53	100	44	96	58.8%	1.16 [0.87, 1.54]
Dolecek 2009	8	26	7	30	8.5%	1.32 [0.55, 3.14]
Dubin 2010	0	9	0	11		Not estimable
Total (95% CI)		**533**		**536**	**100.0%**	**1.30 [1.02, 1.67]**
Total events	100		76			

Heterogeneity: Chi² = 1.23, df = 2 (P = 0.54); I² = 0%

Test for overall effect: Z = 2.11 (P = 0.03)



Trial sequential analysis of severe adverse reactions



We calculated a diversity-adjusted information size of 1798 patients using α = 0.05 (two-sided), β = 0.20 (power = 80%), D^2= 0%, an anticipated relative risk increase of 35% and an event proportion of 14% in the control arm. The cumulative z-curve (blue) was constructed using a fixed-effects model. One trials with no events were included in the analysis with an empirical continuity correction of 0.01.The required information size was not reached and the z-curve crossed the conventional boundary, but not the trial sequential monitoring boundary for harm. The TSA adjusted confidence interval was 0.93 to 1.83.